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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BURKHART, MICHAEL D	

ART UNIT	PAPER NUMBER
1633	

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12/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/031,008	LIBUTTI ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11/16/2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *2,4,16,18,22 and 40*.
   Claim(s) withdrawn from consideration: *3,5-15,17,19,23-37 and 39*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Michael Burkhart/
Primary Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because:
Claims 2, 4, 16, 18, 22 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (U.S. patent 6,638,502, of record) in view of Restifo et al (U.S. patent 5,733,548, of record). This rejection is maintained for reasons made of record in the Office Actions dated 2/22/2006, 11/9/2006, 6/13/2007, 2/8/2008, 11/13/2008, 4/8/2009, 9/16/2009 and for reasons set forth below.
Response to Arguments
Applicant's arguments filed 11/16/2009 have been fully considered but they are not persuasive. To the extent applicants arguments have not been addressed in the previous seven (7) Office Actions set forth above, they are addressed below. Applicants essentially reiterate the points made by the Examiner in the last Office Action and respond to each, they are as follows: 1) the results of the instant invention are surprising in light of the teachings of Gabathuler et al regarding the E3/19K protein; 2) Restifo et al involve targeting a peptide to the ER in order to associate it with MHC molecules, producing a complex that is displayed on the cell surface and thus not secreted; 3) the art does not hint that proteins attached to an E19 signal sequence would be secreted; 4) Li et al teach that the signal sequence is not the E19 signal sequence; 5) the present rejection is based upon the assumption that all signal sequences are the same, which is contradicted by the prior art; 6) Neither Restifo nor Li et al teach that the E19 signal sequence will predictably express a secreted form of an antiangiogenic protein commensurate in scope with the claims; 7) nothing in the prior art suggest arriving at a composition that reduces tumor growth when administered systemically; 8) Griscelli et al does make up for the deficiencies of Restifo and Li et al.

Regarding 1) - 3), applicants continue to mistakenly assert that the ER is not a part of the secretory pathway, thus, merely using a signal sequence to direct proteins into the ER is not to be considered directing them into the secretory pathway. It is unclear what the reasoning for this assertion is based upon, given the extensive teachings of the prior art made of record which show the ER is an integral, necessary compartment of the secretory pathway. Directing proteins into the ER is necessary for secretion in nearly all cases, and is also sufficient if the protein has no further signals (e.g. an ER retention signal). See the teachings of Alberts (linking pages 600-601, of record) regarding the default secretion pathway: basically, once in the ER, if a protein does not have any further signals recognized by the secretory pathway, it is secreted. This is basic information found in a textbook published in 1994 and is undisputed by any reasoning or facts presented by applicants. Applicants discussion of a defective retention signal by Gabathuler et al is confusing because such a signal is not found in the claims, is not used in the prior art, and was a basis for the instant rejection. The relevance of this assertion is also unclear because the claimed invention and the signal sequence of the E3 protein used by Restifo et al do not involve the retention signal. This appears to be a problem not recognized by the prior art and invented by applicants to confuse the issue. There are no teachings or suggestion in the prior art to include the E3 ER retention signal in any chimeric proteins.
Applicants assertion that MHC molecules are responsible for directing the E3 protein, or the peptides of Restifo et al, to the secretory pathway is also unfounded. A review of the art of record reveals no such teachings. MHC molecules are processed through the same pathway (i.e. the default pathway as taught in Alberts et al) as other secreted proteins and are maintained on the cell surface due to their transmembrane domain. They form a complex with peptides (that do not typically have a secretion signal) found in the ER, then are transported to the cell surface via the secretory pathway. There is no evidence that MHC molecules are required for the transport of any larger proteins destined for export, e.g. the fusion proteins of Li et al or those of the instant claims.
Gabathuler et al was not relied upon to teach any limitations of the instant claims, as applicants appear to assert. It is a reference provided by applicants. Likewise, applicants continually discuss the role of MHC molecules in the transport of peptides, two topics not even recited in the instant claims and not used for any basis of the instant rejection. This is an attempt to cloud the real issue: that the instant invention used known protein elements for their known function. All of the facts and evidence of the prior art indicate that a signal sequence is sufficient to direct secretion of a given protein absent any other signal recognized by the secretory pathway. Thus, upon using the E3 signal sequence in a chimeric protein, one of skill in the art would expect secretion of the chimeric protein via the secretory pathway. This is a predictable, known technology subject to review articles and textbook chapters (of record) and thus requires no innovation on the part of the skilled artisan.

Regarding 4), it is stipulated, again, that Li et al do not teach the E3 signal sequence. Otherwise this would be a 35 US 102 rejection. Li et al bolsters the case of this rejection, as Li et al appears to teach the varied use of signal sequences to direct the secretion of various antiangiogenic proteins: merely directing the proteins to the secretory pathway via a signal sequence is all that is required (see the discussion above, and, again, the default pathway of Alberts et al). Applicants assertion that there are no teachings of using the E3 signal sequence to direct anything but peptides to the ER is, again, false on its face. It has been repeatedly pointed out that Restifo et al teach the use of the E3 signal sequence to direct secretion of peptides up to 1000 amino acids in length (col. 4). Because many proteins are less than 1000 residues in length, Restifo et al is considered to teach the use of the E3 signal sequence to direct secretion of proteins as well as peptides. Furthermore, Restifo et al also teach the interchangeability of signal sequences: see col. 4, lines 9-31.
Regarding 5), the analysis of the totality of the prior art regarding the use of signal sequences to direct secretion of heterologous proteins stands. There is no basis for applicants assertion that the use of known signal sequences to direct the secretion of known proteins is unpredictable. That signal sequences vary in length, amino acid sequence and efficiency is, again, stipulated. However, applicants have yet to offer a single, concrete, reasonable barrier to the predictable use of such as claimed and taught by the prior art. The E3 signal sequence was a "known option" for the secretion of heterologous proteins in human cells (i.e. a predictable solution), and thus fits into the facts of KSR. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).
Regarding 6), In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the results of Example III) are not recited in the rejected claim(s). Although the claims are

interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).
Furthermore, the instant claims are not method claims. An extensive analysis of why the combination of Li and Restifo et al meet the intended use limitations of claim 40 has been provided, i.e. the compound rendered obvious by these references would provide increased levels of an antiangiogenic protein relative to situations wherein no compound is administered, and such antiangiogenic proteins are known in the art to reduce tumor growth.

Regarding 7), again, this is an intended use limitation and has been addressed previously. Applicants present a page of arguments regarding this issue, but, again, nothing in these arguments details what exactly the structural limitation imposed by this intended use might be. A review of the prosecution reveals the Examiner has not confused structural with functional language in any instance, and has consistently addressed all structural limitations of the claims. The compound thus rendered obvious by the prior art thus necessarily has all functional limitations, as they are the same compound. It is again noted applicants are silent regarding any further structural limitations imposed by the recited intended use that have not been addressed. If, as applicants allege, the Examiner is confused, than it should be very easy to explain what the additional structural limitations might be. Applicants have been given ample opportunity to do so but have consistently declined, instead, offering explanations not relevant to claims directed to compounds (e.g. "the prior art does not teach this method step").

Regarding 8), Griscelli et al is relevant to the instant claims, despite applicants protests to the contrary. The teachings therein are of record and provide evidence to the predictability of decreasing tumor size using a variant of the claimed compound. That Griscelli et al does not teach certain aspects of the claimed invention is stipulated: a review of the prosecution history reveals it is not used to teach any limitations of the instant claims. Applicants assertions that Griscelli et al does not make up for the deficiencies of Restifo and Li et al is thus unconvincing as Griscelli et al is not relied upon to teach any claim limitations. Likewise, applicants assertions that the results of Griscelli et al are irrelevant to the instant rejection are unconvincing in light of the highly related teachings of Griscelli and Li et al, and the lack of any scientific reasoning or facts..